PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07F 7/08, 7/18 | A1

(11) International Publication Number: WO 96/40691

(43) International Publication Date: 19 December 1996 (19.12.96)

(21) International Application Number: PCT/US96/09163

(22) International Filing Date: 4 June 1996 (04.06.96)

(30) Priority Data:

08/483,130	7 June 1995 (07.06.95)	US
08/478,706	7 June 1995 (07.06.95)	US

(60) Parent Applications or Grants
(63) Related by Continuation

US	08/478,706 (CON)
Filed on	7 June 1995 (07.06.95)
US	08/483,130 (CON)
Filed on	7 June 1995 (07.06.95)

(71) Applicant *(for all designated States except US)*: ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: AIKINS, James, A. [GH/US]; Apartment B, 8483 Treeline Drive, Indianapolis, IN 46256 (US). MILLER, Randal, S. [US/US]; 4623 Brighton Court, Lafayette, IN 47905 (US). ZHANG, Tony, Y. [CN/US]; 12345 Moon River Court, Indianapolis, IN 46236 (US).

(74) Agent: STRODE, Janelle, D.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: VINYL SULFOXIDES AND A PROCESS FOR THEIR SYNTHESIS

(57) Abstract

The present invention is directed to new diarylvinyl sulfoxides and to a new process for their synthesis.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgystan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic			SE	Sweden
CG	Congo	KR	Republic of Korea	SG	Singapore
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LR	Liberia	SZ	Swaziland
CS	Czechoslovakia	LT	Lithuania	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	LV	Latvia	TJ	Tajikistan
DK	Denmark	MC	Monaco	TT	Trinidad and Tobago
EE	Estonia	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	UG	Uganda
FI	Finland	ML	Mali	US	United States of America
FR	France	MN	Mongolia	UZ	Uzbekistan
GA	Gabon	MR	Mauritania	VN	Viet Nam

Vinyl Sulfoxides And A Process For Their Synthesis

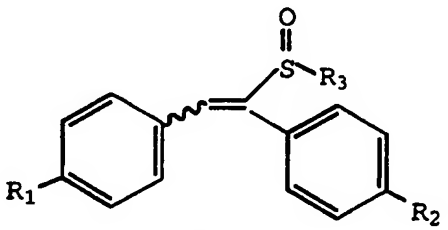
The present invention is directed to novel vinyl sulfoxides and to a new process for the synthesis of same, in particular diarylvinyl sulfoxides. These compounds are useful for the synthesis of benzo[b]thiophenes.

Benzo[b]thiophenes have been prepared by a number of different synthetic routes. One of the most widely used methods is the oxidative cyclization of *o*-mercaptocinnamic acids. This route is limited to the preparation of benzo[b]-thiophene-2-carboxylates. 2-Phenylbenzo[b]thiophenes are prepared by acid-catalyzed cyclization of 2-phenylthioacetaldehyde dialkyl acetals. Unsubstituted benzo[b]thiophenes are prepared by catalytic condensation of styrene and sulfur. 3-Substituted benzo[b]thiophenes are prepared by acid-catalyzed cyclization of arylthiomethyl ketones; however, this route is limited to the preparation of 3-alkylbenzo[b]thiophenes. *See* Campaigne, "Thiophenes and their Benzo Derivatives: (iii) Synthesis and Applications," in **Comprehensive Heterocyclic Chemistry** (Katritzky and Rees, eds.), Volume IV, Part III, 863-934 (1984). 3-Chloro-2-phenylbenzo[b]thiophene is prepared by the reaction of diphenylacetylene with sulfur dichloride. Barton and Zika, *J. Org. Chem.*, **35**, 1729-1733 (1970). Benzo[b]thiophenes have also been prepared by pyrolysis of styryl sulfoxides. However, low yields and extremely high temperatures make this route unsuitable for production-scale syntheses. *See* Ando, *J. Chem. Soc.*, Chem. Comm., 704-705 (1975).

The preparation of 6-hydroxy-2-(4-hydroxyphenyl)benzo-[b]thiophenes was described in U.S. Patent Nos. 4,133,814 and 4,380,635. One process described in these patents is the acid-catalyzed intramolecular cyclization/rearrangement of α -(3-methoxyphenylthio)-4-methoxyacetophenone. The reaction of this starting compound in neat polyphosphoric acid at about 85°C to about 90°C gives an approximate 3:1 mixture of two regioisomeric products: 6-methoxy-2-(4-methoxyphenyl)-benzo[b]thiophene and 4-methoxy-2-(4-methoxyphenyl)benzo[b]-

thiophene. These isomeric benzo[b]thiophenes co-precipitate from the reaction mixture, producing a mixture containing both compounds. To obtain a single regioisomer, the regioisomers must be separated, such as by chromatography or fractional crystallization. Therefore, there currently exists a need for an efficient and regiospecific synthesis of 2-arylbenzo[b]thiophenes from readily available starting materials. The compounds of the present invention are useful for the efficient and regiospecific synthesis of 2-arylbenzo-[b]thiophenes from readily available starting materials.

The present invention is directed to novel vinyl sulfoxides and to a new process for their synthesis, in particular diarylvinyl sulfoxides. Specifically, the present invention is directed to a compound of the formula



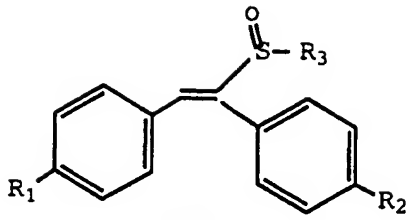
II

wherein:

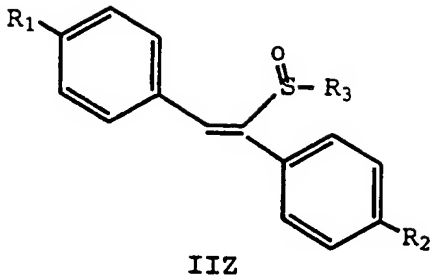
R_1 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino;

R_2 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino; and

R_3 is a thermally-labile or acid-labile C_2-C_{10} alkyl, C_4-C_{10} alkenyl, or aryl(C_1-C_{10} alkyl) group. Thus, the present invention includes individually the **E** and **Z** isomers, or mixtures thereof, of the formula II compounds. These **E** and **Z** regioisomers are represented by the following structures:

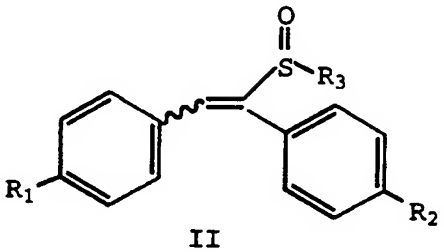


IIE



IIZ

Another aspect of the present invention is a process for preparing a compound of the formula



II

wherein:

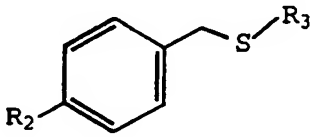
R_1 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino;

R_2 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino; and

R_3 is a thermally-labile or acid-labile C_2-C_{10} alkyl, C_4-C_{10} alkenyl, or aryl(C_1-C_{10} alkyl) group having a tertiary carbon atom adjacent to the sulfur atom;

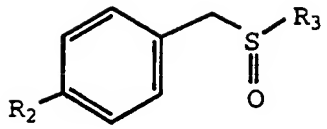
comprising the steps of:

(1) oxidizing a benzyl sulfide of the formula:



wherein R_2 and R_3 are as defined above;

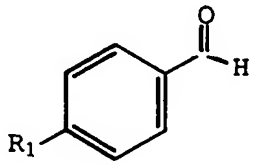
with an oxidizing agent to produce a benzyl sulfoxide of the formula:



wherein R_2 and R_3 are as defined above;

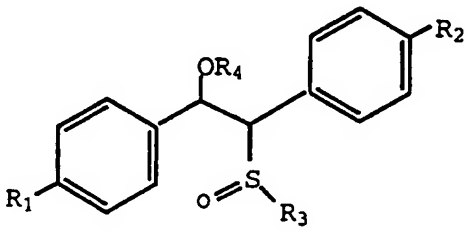
(2) reacting said benzyl sulfoxide with a strong base to form a benzylic anion;

(3) condensing said benzylic anion with a benzaldehyde of the formula



wherein R_1 is as defined above;

(4) reacting the condensation product from step 3 with an acid chloride to produce an ester of the formula



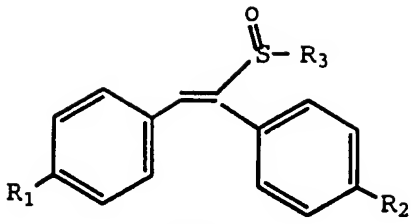
wherein:

R_1, R_2, and R_3 are as defined above; and

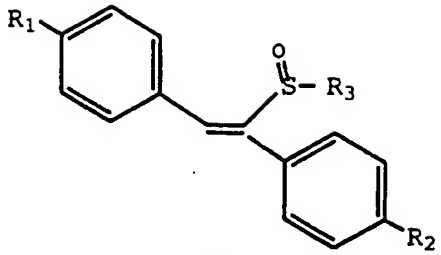
R_4 is $CO(C_1\text{-}C_6$ alkyl), CO(aryl), CO(arylalkyl), $SO_2(C_1\text{-}C_6$ alkyl), SO_2(aryl), SO_2(arylalkyl), $CO_2(C_1\text{-}C_6$ alkyl), CO_2(aryl), CO_2(arylalkyl), or $CON(C_1\text{-}C_6$ alkyl$)_2$; and

(5) treating said ester with a second strong base.

The **E** and **Z** regioisomers the formula II compounds are represented by the following structures:

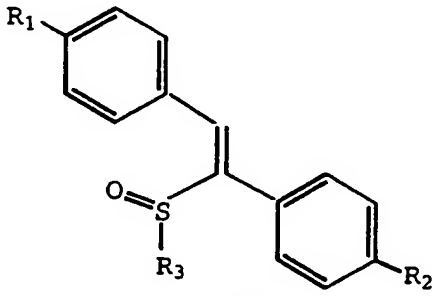


IIE



IIZ

Another aspect of the present invention is a process for the regioselective synthesis of the Z isomer of the formula II compounds. In particular, the present invention relates to a process for preparing a compound of the formula



IIZ

wherein:

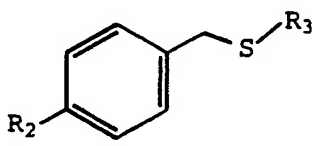
R_1 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino;

R_2 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino; and

R_3 is a thermally-labile or acid-labile C_2-C_{10} alkyl, C_4-C_{10} alkenyl, or aryl(C_1-C_{10} alkyl) group having a tertiary carbon atom adjacent to the sulfur atom;

comprising the steps of:

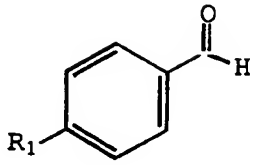
(1) reacting a benzyl sulfide of the formula:



wherein R_2 and R_3 are as defined above;

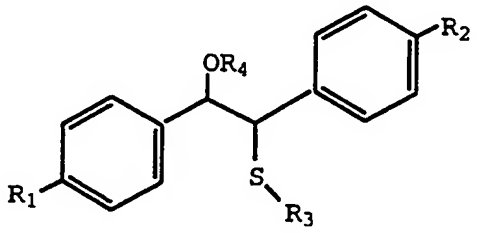
with a strong base to form a benzylic anion;

(2) condensing said benzylic anion with a benzaldehyde of the formula



wherein R_1 is as defined above;

(3) reacting the condensation product from step 2 with an acid chloride to produce an ester of the formula

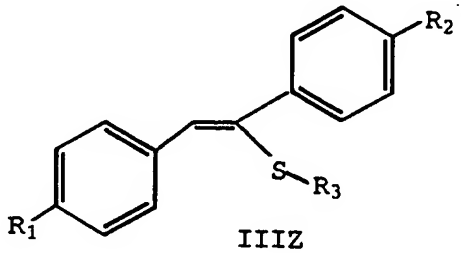


wherein:

R_1, R_2, and R_3 are as defined above; and

R_4 is $CO(C_1-C_6$ alkyl), CO(aryl), CO(arylalkyl), $SO_2(C_1-C_6$ alkyl), SO_2(aryl), SO_2(arylalkyl), $CO_2(C_1-C_6$ alkyl), CO_2(aryl), CO_2(arylalkyl), or $CON(C_1-C_6$ alkyl$)_2$;

(4) treating said ester with a second strong base to produce a styryl sulfide of the formula

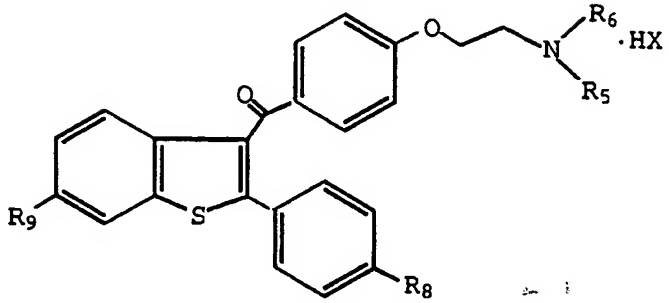


IIIZ

wherein R_1, R_2, and R_3 are as defined above; and

(5) oxidizing said styryl sulfide with an oxidizing agent.

Yet another aspect of the present invention is a process for the synthesis of a compound of the formula



XII

wherein:

R_8 is hydrogen, halo, amino, or hydroxyl;

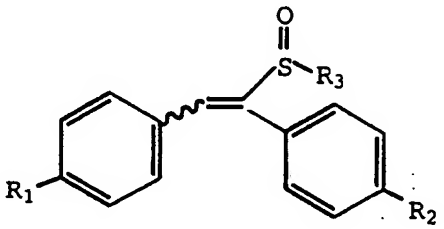
R_9 is hydrogen, halo, amino, or hydroxyl;

R_5 and R_6 are independently C_1-C_4 alkyl, or R_5 and R_6 together with the adjacent nitrogen atom form a heterocyclic ring selected from the group consisting of pyrrolidino, piperidino, hexamethyleneimino, and morpholino; and

HX is HCl or HBr;

comprising the steps of:

(a) cyclizing in the presence of an acid catalyst a compound of the formula



II

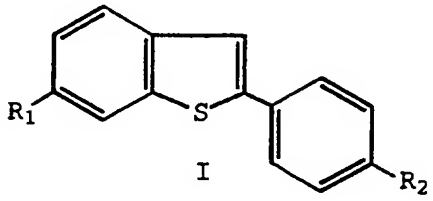
wherein:

R_1 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino;

R_2 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino; and

R_3 is a thermally-labile or acid-labile C_2-C_{10} alkyl,

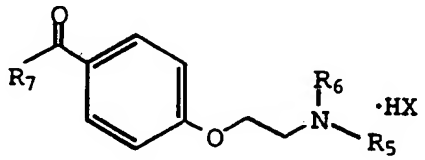
C_4-C_{10} alkenyl, or aryl(C_1-C_{10} alkyl) group to prepare a benzothiophene compound of the formula



I

wherein R_1 and R_2 are as defined above;

(b) acylating said benzothiophene compound with an acylating agent of the formula



wherein:

R_5, R_6, and HX are as defined previously; and

R_7 is chloro, bromo, or hydroxyl; in the presence of BX'_3, wherein X' is chloro or bromo;

(c) when R_1 and/or R_2 is C_1-C_4 alkoxy or arylalkoxy, dealkylating one or more phenolic groups of the acylation product of step (b) by reacting with additional BX'_3, wherein X' is as defined above; and

(d) isolating the formula XII compound.

The term "C_1-C_6 alkyl" represents a straight or branched alkyl chain having from one to six carbon atoms. Typical C_1-C_6 alkyl groups include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *t*-butyl, *n*-pentyl, isopentyl, *n*-hexyl, 2-methylpentyl, and the like. The term "C_1-C_4 alkyl" represents a straight or branched alkyl chain having from one

to four carbon atoms, and includes methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, *i*-butyl, and *t*-butyl.

The term "C_1-C_4 alkoxy" represents groups such as methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *t*-butoxy, and like groups. The term "halo" refers to fluoro, chloro, bromo, or iodo groups.

The term "aryl" represents groups such as phenyl and substituted phenyl. The term "substituted phenyl" represents a phenyl group substituted with one or more moieties chosen from the group consisting of halo, hydroxy, nitro, C_1-C_4 alkyl, C_1-C_4 alkoxy, trichloromethyl, and trifluoromethyl. Examples of a substituted phenyl group include 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 3-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2-fluorophenyl, 4-hydroxyphenyl, 3-hydroxyphenyl, 2,4-dihydroxyphenyl, 3-nitrophenyl, 4-nitrophenyl, 2,4-dinitrophenyl, 4-methylphenyl, 4-ethylphenyl, 4-methoxyphenyl, 4-propylphenyl, 4-*n*-butylphenyl, 4-*t*-butylphenyl, 3-fluoro-2-methylphenyl, 2,3-difluorophenyl, 2,6-difluorophenyl, 2,6-dimethylphenyl, 2-fluoro-5-methylphenyl, 2,4,6-trifluorophenyl, 2-trifluoromethylphenyl, 2-chloro-5-trifluoromethylphenyl, 3,5-bis(trifluoromethyl)phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 3,5-dimethoxyphenyl, 4-hydroxy-3-methylphenyl, 3,5-dimethyl, 4-hydroxyphenyl, 2-methyl-4-nitrophenyl, 4-methoxy-2-nitrophenyl, and the like.

The term "arylalkyl" represents a C_1-C_4 alkyl group bearing one or more aryl groups. Representatives of this group include benzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl (such as *p*-chlorobenzyl, *p*-bromobenzyl, *p*-iodobenzyl), 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 2-methyl-2-phenylpropyl, (2,6-dichlorophenyl)methyl, bis(2,6-dichlorophenyl)methyl, (4-hydroxyphenyl)methyl, (2,4-dinitrophenyl)methyl, diphenylmethyl, triphenylmethyl, (*p*-methoxyphenyl)-diphenylmethyl, bis(*p*-methoxyphenyl)methyl, bis(2-nitrophenyl)methyl, and the like.

The term "arylalkoxy" represents a C_1-C_4 alkoxy group bearing one or more aryl groups. Representatives of this group include benzyloxy, *o*-nitrobenzyloxy, *p*-nitrobenzyloxy, *p*-halobenzyloxy (such as *p*-chlorobenzyloxy, *p*-bromobenzyloxy, *p*-iodobenzyloxy), 1-phenylethoxy, 2-phenylethoxy, 3-phenylpropoxy, 4-phenylbutoxy, 2-methyl-2-phenylpropoxy, (2,6-dichlorophenyl)methoxy, bis(2,6-dichlorophenyl)methoxy, (4-hydroxyphenyl)methoxy, (2,4-dinitrophenyl)methoxy, diphenylmethoxy, triphenylmethoxy, (*p*-methoxyphenyl)-diphenylmethoxy, bis(*p*-methoxyphenyl)methoxy, bis(2-nitrophenyl)methoxy, and the like.

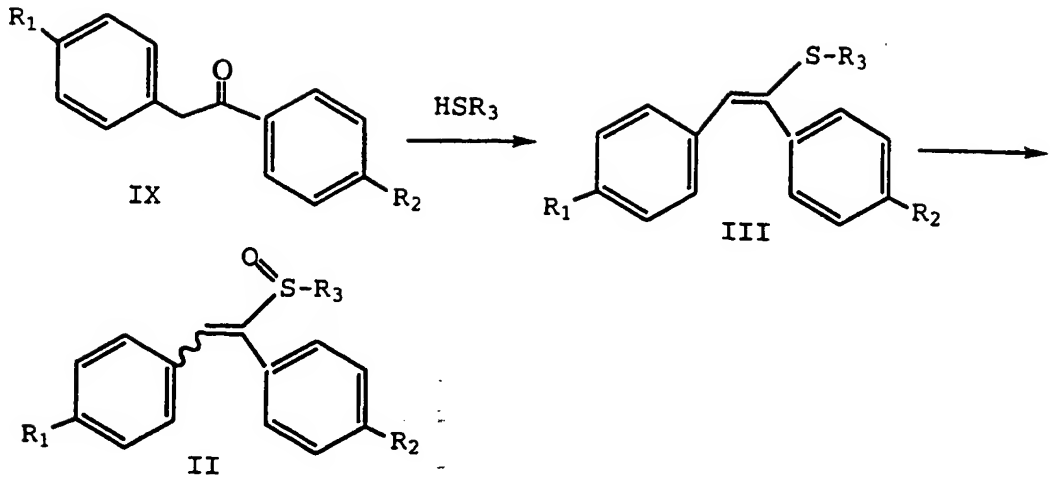
The term "thermally-labile or acid-labile C_2-C_{10} alkyl, C_4-C_{10} alkenyl, or aryl(C_1-C_{10} alkyl) group" represents a group that is readily removed from the sulfoxide (SO) group under heating or by treatment with the acid catalyst. The thermally-labile or acid-labile C_2-C_{10} alkyl groups are straight or branched alkyl chains having from two to ten carbon atoms and having at least one beta-hydrogen atom. Representative thermally-labile or acid-labile C_2-C_{10} alkyl groups include ethyl, *n*-propyl, *i*-propyl, 1,1-dimethyl-propyl, *n*-butyl, *sec*-butyl, *t*-butyl, 1,1-dimethylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,4-dimethylbutyl, 3,3-dimethylbutyl, *n*-pentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, *n*-hexyl, and the like. The thermally-labile or acid-labile C_4-C_{10} alkenyl groups are straight or branched alkenyl chains having from four to ten carbon atoms, at least one site of unsaturation, and either a beta-hydrogen or delta-hydrogen atom. Representative thermally-labile or acid-labile C_4-C_{10} alkenyl groups include 2-butenyl, 3-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 2-methyl-3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-methyl-2-pentenyl, 3-methyl-2-pentenyl, 4-methyl-2-pentenyl, 2-methyl-3-pentenyl, 3-methyl-3-pentenyl, 4-methyl-3-pentenyl, 2-methyl-4-pentenyl, 3-methyl-4-pentenyl, 4-methyl-4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, and the like. The term thermally-labile or acid-labile aryl(C_1-C_{10} alkyl)

represents thermally-labile or acid-labile C_2-C_{10} alkyl groups additionally containing one or more aryl groups and aryl-substituted methyl groups. Representative aryl(C_1-C_{10} alkyl) groups include benzyl, diphenylmethyl, triphenylmethyl, *p*-methoxybenzyl, 2-phenylethyl, 2-phenyl-propyl, 3-phenyl-propyl, and the like. The term "thermally-labile or acid-labile C_2-C_{10} alkyl, C_4-C_{10} alkenyl, or aryl(C_1-C_{10} alkyl) group having a tertiary carbon atom adjacent to the sulfur atom" includes, but is not limited to, such groups as *t*-butyl, 1,1-dimethylpropyl, 1,1-dimethylbutyl, 1-ethyl-1-methylpropyl, 1,1-dimethylpentyl, 1-ethyl-1-methylbutyl, 1,1-diethylpropyl, 1,1-dimethylhexyl, triphenylmethyl, and the like.

The term "acid chloride" includes acyl chlorides, such as acetyl chloride and benzoyl chloride; sulfonyl chlorides, such as methanesulfonyl chloride, benzenesulfonyl chloride, 1-butanesulfonyl chloride, ethanesulfonyl chloride, isopropylsulfonyl chloride, and *p*-toluenesulfonyl chloride; alkoxycarbonyl chlorides, such as methoxycarbonyl chloride and benzyloxycarbonyl chloride; and dialkylaminocarbonyl chlorides, such as *N,N*-dimethylaminocarbonyl chloride. Preferably the acid chloride is a sulfonyl chloride. More preferably, the acid chloride is methanesulfonyl chloride.

The compounds of the present invention can be prepared by a number of routes. One method for preparing the formula II compounds is shown in Scheme 1.

Scheme 1



Generally, a formula IX compound is converted to a styryl sulfide by reaction with a mercaptan of the formula HSR_3 in the presence of a Lewis acid. The formula III compound is then oxidized to a styryl sulfoxide, a compound of formula II compound.

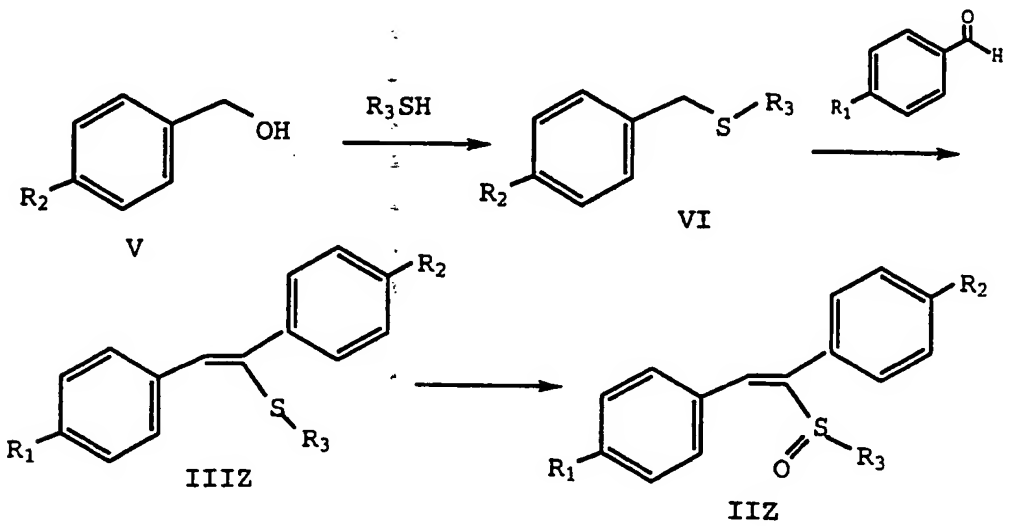
More specifically, a formula IX compound, wherein R_1 and R_2 are as defined above, is treated with a Lewis acid, such as titanium(IV) chloride. This reaction is carried out in an anhydrous organic solvent, such as dry tetrahydrofuran, at a temperature of about 0°C to about 35°C. After about fifteen minutes to about one hour, the reaction mixture is treated with an amine base and a mercaptan of the formula HSR_3, where R_3 is as defined above. Preferably, the mercaptan and amine base are added as a solution in the reaction solvent. A representative amine base is triethylamine. After the addition of the mercaptan and amine base, the reaction is generally heated to a temperature of about 35°C to about 65°C, preferably at about 50°C. The products of this reaction can be purified using techniques well known in the chemical arts, such as by crystallization or chromatography.

The formula III compound, where R_1, R_2, and R_3 are as defined above, is then oxidized to produce the formula II compounds. Suitable oxidizing agents for this reaction are peracids, such as peracetic acid and *m*-chloroperoxybenzoic

acid, and hydrogen peroxide. This oxidation reaction is typically run in an organic solvent, such as toluene, methylene chloride, chloroform, or carbon tetrachloride. When a peracid is used as the oxidant, the reaction is generally carried out at a temperature of about -30°C to about 15°C, preferably at about -20°C. The products of the reaction are easily purified by recrystallization. When R_3 is *t*-butyl, the crystalline product of this reaction sequence is the **E** regioisomer of formula II.

When R_3 has a tertiary carbon adjacent to the sulfur atom, the **Z** regioisomer of the formula II compounds can be prepared selectively by a route as shown in Scheme 2.

Scheme 2



Generally, a benzyl alcohol, a formula V compound, is reacted with a mercaptan of the formula R_3SH to produce a benzyl sulfide, a formula VI compound. This benzyl sulfide is reacted with a strong base, forming a benzylic anion, which is condensed with a benzaldehyde. This condensation product is reacted with an acid chloride and the resulting intermediate ester treated with a second strong base to produce a styryl sulfide, a formula IIIZ compound. This

styryl sulfide is then oxidized with an oxidizing agent to produce the formula IIZ compound.

The first step in the synthesis of the Z styryl sulfoxide compounds is the conversion of a benzyl alcohol to a benzyl sulfide, formula VI compound. The reaction of the formula V compound, where R_2 is as defined above, with a mercaptan of the formula R_3SH, wherein R_3 is a thermally-labile or acid-labile C_2-C_{10} alkyl, C_4-C_{10} alkenyl, or aryl(C_1-C_{10} alkyl) group having a tertiary carbon atom adjacent to the sulfur atom, in the presence of a Lewis acid produces the benzyl sulfide, a formula VI compound. Suitable Lewis acids for this transformation are zinc bromide, zinc chloride, zinc iodide, ferric chloride, titanium(IV) chloride, aluminum trichloride, and aluminum tribromide, preferably zinc iodide. The reaction is generally carried out in an organic solvent, such as 1,2-dichloroethane or methylene chloride. When the reaction is carried out at room temperature, the reaction is complete after about 18 hours.

The benzyl sulfide is reacted with a strong base to form a benzylic anion. Suitable strong bases for this reaction include metal alkoxides, such as sodium methoxide, sodium ethoxide, lithium ethoxide, lithium *t*-butoxide, and potassium *t*-butoxide; sodium hydride; and alkyllithiums, such as *n*-butyllithium, *t*-butyllithium, *sec*-butyllithium, and methyllithium. The preferred strong base for this reaction is *n*-butyllithium. The preferred solvent for this reaction is dry tetrahydrofuran. When *n*-butyllithium is used as the strong base, the reaction is carried out at a temperature of about -35°C to about -15°C.

The benzylic anion is condensed with a benzaldehyde to prepare an intermediate condensation product. The benzaldehyde has the general formula $R_1(C_6H_4)CHO$, wherein R_1 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino. Preferably, the benzylic anion is prepared and the condensation product is formed *in situ* by adding the benzaldehyde to the cold solution of the benzylic anion.

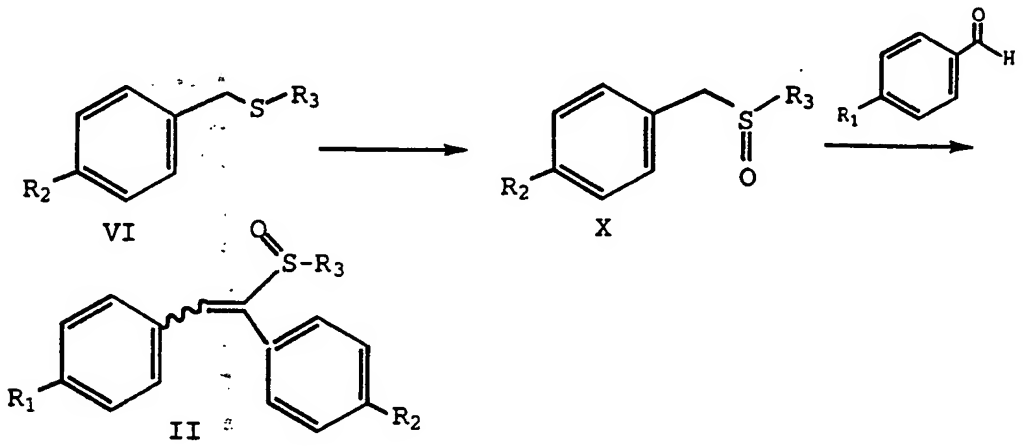
The condensation product is treated with an acid chloride to produce an intermediate ester. Representative acid chlorides include acyl chlorides, such as acetyl chloride and benzoyl chloride; sulfonyl chlorides, such as methanesulfonyl chloride, benzenesulfonyl chloride, 1-butanesulfonyl chloride, ethanesulfonyl chloride, isopropylsulfonyl chloride, and *p*-toluenesulfonyl chloride; alkoxycarbonyl chlorides, such as methoxycarbonyl chloride and benzyloxycarbonyl chloride; and dialkylaminocarbonyl chlorides, such as *N,N*-dimethylaminocarbonyl chloride; preferably a sulfonyl chloride. Preferably, methanesulfonyl chloride is added to the reaction mixture shortly after formation of the condensation product.

This intermediate ester is reacted with a second strong base to produce a styryl sulfide, a formula IIIZ compound where R_1, R_2, and R_3 are as defined above. Suitable strong bases for this reaction include metal alkoxides, such as sodium methoxide, sodium ethoxide, lithium ethoxide, lithium *t*-butoxide, and potassium *t*-butoxide; sodium hydride; alkyllithiums, such as *n*-butyllithium, *t*-butyllithium, *sec*-butyllithium, and methyllithium; and metal amides, such as sodium amide, magnesium diisopropylamide, and lithium diisopropylamide. The preferred strong base for this reaction is potassium *t*-butoxide. Generally, this reaction is carried out at about 15°C to about room temperature, preferably at room temperature.

The styryl sulfide is oxidized to prepare the corresponding styryl sulfoxide. Suitable oxidizing agents for this reaction are peracids, such as peracetic acid and *m*-chloroperoxybenzoic acid; organic peroxides, such as *t*-butyl peroxide; and hydrogen peroxide. Preferably the oxidizing agent is peracetic acid. This oxidation is typically carried out in an organic solvent, such as toluene, benzene, xylene, methanol, ethanol, methylacetate, ethylacetate, methylene chloride, 1,2-dichloroethane, or chloroform; preferably methylene chloride. This oxidation can be carried out at a temperature of about -40°C to about 0°C.

Alternatively, when R_3 has a tertiary carbon adjacent to the sulfur atom, the benzyl sulfide intermediate (formula VI compound) can be used to produce a mixture of **E** and **Z** isomers of the styryl sulfoxides, the formula II compounds. This synthesis is outlined in Scheme 3.

Scheme 3



The benzyl sulfide, prepared as described above, is oxidized to produce the corresponding benzyl sulfoxide. This benzyl sulfoxide is reacted with a strong base, and the resulting anion condensed with a benzaldehyde. The condensation product is reacted with an acid chloride and the resulting intermediate ester reacted with a second strong base to produce the styryl sulfoxide.

The benzyl sulfide, the formula VI compound, wherein R_2 is as defined above and R_3 is a thermally-labile or acid-labile C_2-C_{10} alkyl, C_4-C_{10} alkenyl, or aryl(C_1-C_{10} alkyl) group having a tertiary carbon atom adjacent to the sulfur atom, is oxidized to produce the corresponding benzyl sulfoxide, formula X compound. Suitable oxidizing agents for this reaction are peracids, such as peracetic acid and *m*-chloroperoxybenzoic acid; organic peroxides, such as *t*-butyl peroxide; and hydrogen peroxide. Preferably the oxidizing agent is peracetic acid. This oxidation is typically carried

out in an organic solvent, such as toluene, benzene, xylene, methanol, ethanol, methylacetate, ethylacetate, methylene chloride, 1,2-dichloroethane, or chloroform; preferably at a temperature of about -30°C to about 5°C.

The benzyl sulfoxide, formula X compound wherein R_2 and R_3 are as defined above, is reacted with a strong base to produce a benzylic anion. Suitable strong bases for this reaction include metal alkoxides, such as sodium methoxide, sodium ethoxide, lithium ethoxide, lithium *t*-butoxide, and potassium *t*-butoxide; sodium hydride; alkyllithiums, such as *n*-butyllithium, *t*-butyllithium, *sec*-butyllithium, and methyllithium; and metal amides, such as sodium amide, magnesium diisopropylamide, and lithium diisopropylamide. The preferred base for this transformation is *n*-butyllithium. This deprotonation reaction is carried out in a dry organic solvent, such as tetrahydrofuran or 1,2-dimethoxyethane, at a temperature of about -25°C.

The benzylic anion is condensed, without isolation, with a benzaldehyde compound of the formula *p*-$R_1(C_6H_4)CHO$, wherein R_1 is as defined above. Preferably, about one equivalent of the benzaldehyde is added to the cold solution prepared as described in the preceding paragraph. The resulting diastereomeric mixture of condensation products may be isolated, or preferably used in the next step without isolation.

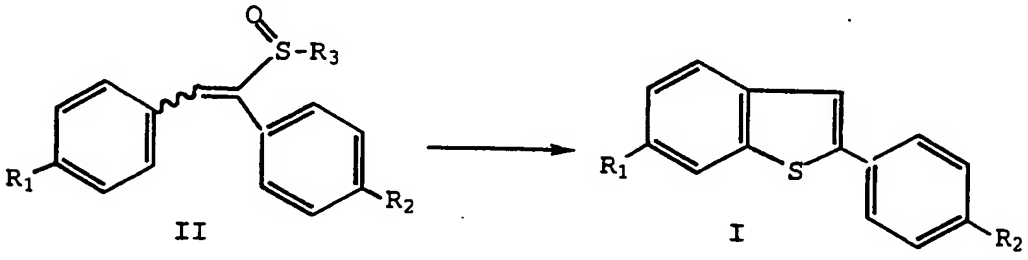
The condensation product is optionally treated with a base, such as *n*-butyllithium, and reacted with an acid chloride. Representative acid chlorides include acyl chlorides, such as acetyl chloride and benzoyl chloride; sulfonyl chlorides, such as methanesulfonyl chloride, benzenesulfonyl chloride, 1-butanesulfonyl chloride, ethanesulfonyl chloride, isopropylsulfonyl chloride, and *p*-toluenesulfonyl chloride; alkoxycarbonyl chlorides, such as methoxycarbonyl chloride and benzyloxycarbonyl chloride; and dialkylaminocarbonyl chlorides, such as *N,N*-dimethylaminocarbonyl chloride; preferably a sulfonyl chloride. The acid chloride is added to the cold reaction

mixture, then the resulting mixture is allowed to warm to room temperature. Preferably, methanesulfonyl chloride is added to the reaction mixture shortly after formation of the condensation product, which eliminates the need to add additional base.

The resulting intermediate ester is reacted with a second strong base to produce the **E** and **Z** styryl sulfoxides, formula II compounds where R_1, R_2, and R_3 are as defined above. Representative second strong bases for this elimination reaction include metal alkoxides, such as sodium methoxide, sodium ethoxide, lithium ethoxide, lithium *t*-butoxide, and potassium *t*-butoxide; sodium hydride; alkyllithiums, such as *n*-butyllithium, *t*-butyllithium, *sec*-butyllithium, and methyllithium; and metal amides, such as sodium amide, magnesium diisopropylamide, and lithium diisopropylamide. The preferred base for this transformation is potassium *t*-butoxide. Preferably, a 20% excess, such as 1.2 equivalents, of the second base are added. Generally, this reaction is carried out at a temperature of about 15°C to about room temperature, preferably at room temperature.

The intermediate styryl sulfoxides are useful for the synthesis of 2-arylbenzo[b]thiophenes as shown in Scheme 4.

Scheme 4



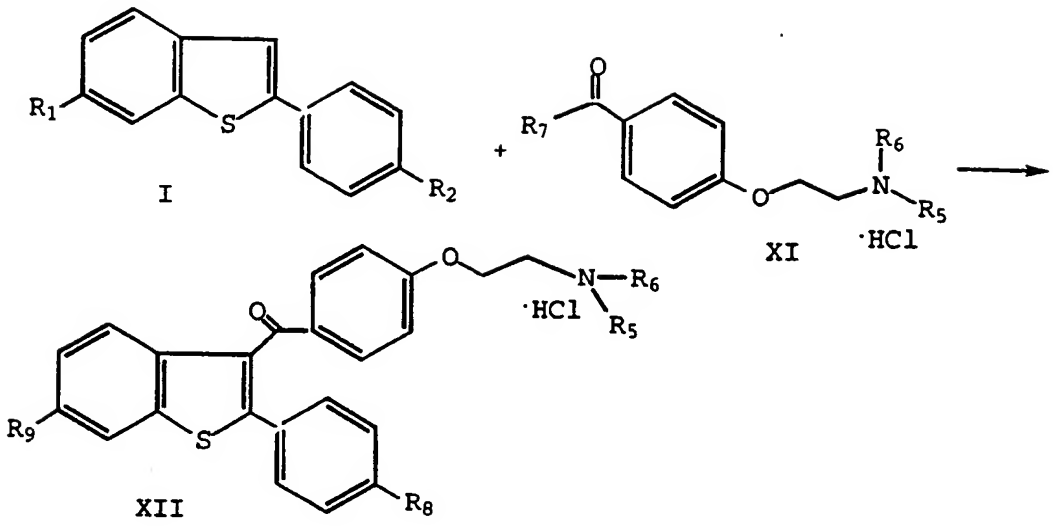
Generally, the intermediate styryl sulfoxide compounds are heated and treated with acid catalysts to produce the formula I compounds. Suitable acid catalysts for this reaction include Lewis acids or Brønsted acids. Representative Lewis acids include zinc chloride, zinc

iodide, aluminum chloride, and aluminum bromide. Representative Brønsted acids include inorganic acids, such as sulfuric and phosphoric acids; carboxylic acids, such as acetic and trifluoroacetic acids; sulfonic acids, such as methanesulfonic, benzenesulfonic, 1-naphthalenesulfonic, 1-butanesulfonic, ethanesulfonic, 4-ethylbenzenesulfonic, 1-hexanesulfonic, 1,5-naphthalenedisulfonic, 1-octanesulfonic, camphorsulfonic, trifluoromethanesulfonic, and *p*-toluene-sulfonic acids; and polymeric arylsulfonic acids, such as Nafion®, Amberlyst®, or Amberlite®. The more preferred acid catalysts are sulfonic acids, such as methanesulfonic acid, benezene-sulfonic acid, camphorsulfonic, and *p*-toluenesulfonic acid. The most preferred acid catalyst is *p*-toluenesulfonic acid. Typically, a solution of the acid catalyst in organic solvent, such as toluene, benzene, xylene, or a high-boiling halogenated hydrocarbon solvents, such as 1,1,2-trichloro-ethane, is heated to about 80° to about 140°C, and treated with a solution of the styryl sulfoxide in the same solvent. An excess amount of the acid catalyst is used, preferably two equivalents of the acid. For best results, the final concentration of the starting compound is about 0.01 M to about 0.2 M, preferably 0.05 M. Furthermore, best yields are obtained when the styryl sulfoxide is slowly added to the heated acid solution over a period of about 20 minutes to about three hours. For best results, residual water is removed from the reaction solution by the use of a Dean-Stark trap or Soxhlet extractor, and the reaction is purged with purified nitrogen.

The formula I compounds are useful as intermediates in the synthesis of a series of 3-aroyl-2-arylbenzo[b]-thiophenes. U.S. Patent Nos. 4,133,814 and 4,418,068, which are incorporated herein by reference, described these 3-aroyl-2-arylbenzo[b]thiophenes, as well as methods for their preparation from the formula I compounds. An improved synthesis of a group of these 3-aroyl-2-arylbenzo[b]-thiophenes from the formula I compounds, wherein R_1 and R_2 are hydrogen, C_1-C_4 alkoxy, or arylalkoxy, is outlined in

Scheme 5.

Scheme 5



The benzothiophene Formula I compound, wherein R_1 and R_2 are hydrogen, C_1-C_4 alkoxy, or arylalkoxy, is acylated with the formula XI compound, wherein R_7 is chloro or hydroxy, in the presence of boron trichloride or boron tribromide; boron trichloride is preferred. The reaction can be carried out in a variety of organic solvents, such as chloroform, methylene chloride, 1,2-dichloroethane, 1,2,3-dichloropropane, 1,1,2,2-tetra-chloroethane, 1,2-dichlorobenzene, chlorobenzene, and fluorobenzene. The preferred solvent for this synthesis is 1,2-dichloroethane. The reaction is carried out at a temperature of about -10°C to about 25°C, preferably at 0°C. The reaction is best carried out at a concentration of the benzothiophene formula I compound of about 0.2 M to about 1.0 M. The acylation reaction is generally complete after about two hours to about eight hours.

When R_1 and/or R_2 is a C_1-C_4 alkoxy or arylalkoxy group, the acylated benzothiophene, is converted to a formula XI compound wherein R_8 and/or R_9 are hydroxy, without isolation of the product from the acylation reaction. This conversion

is performed by adding additional boron trihalide or boron tribromide and heating the reaction mixture. Preferably, two to five molar equivalents of boron trihalide are added to the reaction mixture, most preferably three molar equivalents. This reaction is carried out at a temperature of about 25°C to about 40°C, preferably at 35°C. The reaction is generally complete after about 4 to 48 hours.

The acylation reaction or acylation/dealkylation reaction is quenched with an alcohol or a mixture of alcohols. Suitable alcohols for use in quenching the reaction include methanol, ethanol, and isopropanol. Preferably, the acylation/dealkylation reaction mixture is added to a 95:5 mixture of ethanol and methanol (3A ethanol). The 3A ethanol can be at room temperature or heated to reflux, preferably at reflux. When the quench is performed in this manner, the Formula XII compound conveniently crystallizes from the resulting alcoholic mixture. Generally, 1.25 mL to 3.75 mL of alcohol per millimole of the benzothiophene starting material are used.

The following examples further illustrate the present invention. The examples are not intended to be limiting to the scope of the invention in any respect, and should not be so construed. All experiments were run under positive pressure of dry nitrogen. All solvents and reagents were used as obtained. The percentages are generally calculated on a weight (w/w) basis; except for high performance liquid chromatography (HPLC) solvents which are calculated on a volume (v/v) basis. Proton nuclear magnetic resonance (^{1}H NMR) spectra and ^{13}C nuclear magnetic resonance spectra (^{13}C NMR) were obtained on a Bruker AC-300 FTNMR spectrometer at 300.135 MHz or a GE QE-300 spectrometer at 300.15 MHz. Silica-gel flash chromatography was performed as described by Still *et al.* using Silica Gel 60 (230-400 mesh, E. Merck). Still *et al.*, *J. Org. Chem.*, **43**, 2923 (1978). Elemental analyses for carbon, hydrogen, and nitrogen were determined on a Control Equipment Corporation 440 Elemental Analyzer. Elemental analyses for sulfur were determined on a Brinkman

Colorimetric Elemental Analyzer. Melting points were determined in open glass capillaries on a Mel-Temp II melting point apparatus or a Mettler FP62 Automatic instrument, and are uncorrected. Field desorption mass spectra (FDMS) were obtained using a Varian Instruments VG 70-SE or VG ZAB-3F mass spectrometer. High resolution free atom bombardment mass spectra (FABMS) were obtained using a Varian Instruments VG ZAB-2SE mass spectrometer.

The *in situ* yields of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene were determined by high performance liquid chromatography (HPLC) in comparison to an authentic sample of this compound prepared by published synthetic routes. *See* U.S. Patent No. 4,133,814. Generally, samples of the reaction mixture was diluted with acetonitrile and the diluted sample assayed by HPLC using a Zorbax RX-C8 column (4.6 mm x 25 cm) with UV detection (280 nm). The following linear-gradient solvent system was used for this analysis:

Gradient Solvent System

Time (min)	A (%)	B (%)
0	50	50
2	50	50
20	20	80
35	20	80
37	50	50

45 50 50

A: 0.01 M aqueous sodium phosphate (pH 2.0)
B. acetonitrile

The amount (percentages) of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene hydrochloride in the crystalline material (potency) was determined by the following method. A sample of the crystalline solid (5 mg) was weighed into a 100-mL volumetric flask, and dissolved in a 70/30 (v/v) mixture of

75 mM potassium phosphate buffer (pH 2.0) and acetonitrile. An aliquot of this solution (10 µ L) was assayed by high performance liquid chromatography, using a Zorbax Rx-C8 column (25 cm x 4.6 mm ID, 5 µ particle) and UV detection (280 nm). The following gradient solvent system was used:

Gradient Solvent System (Potency)

Time (min)	A (%)	B (%)
0	70	30
12	70	30
14	25	75
16	70	30
25	70	30

A: 75 mM KH_2PO_4 buffer (pH 2.0)

B: acetonitrile

The percentage of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride in the sample was calculated using the peak area, slope (m), and intercept (b) of the calibration curve with the following equation:

$$\% \text{ potency} = \frac{\text{peak area} - b}{m} \times \frac{\text{sample volume (mL)}}{\text{sample weight (mg)}}$$

The amount (percentage) of solvent, such as 1,2-dichloroethane, present in the crystalline material was determined by gas chromatography. A sample of the crystalline solid (50 mg) was weighed into a 10-mL volumetric flask, and dissolved in a solution of 2-butanol (0.025 mg/mL) in dimethylsulfoxide. A sample of this solution was analyzed on a gas chromatograph using a DB Wax column (30 m x 0.53 mm ID, 1 µ particle), with a column flow of 10 mL/min and flame ionization detection. The column temperature was heated from

35°C to 230°C over a 12 minute period. The amount of solvent was determined by comparison to the internal standard (2-butanol).

Example 1

E-*t*-Butyl 4,4'-Dimethoxystilbenyl Sulfoxide

A. Preparation of **E-*t*-Butyl 4,4'-Dimethoxystilbenyl Sulfide**

A solution of desoxyanisoin (12.82 g) in tetrahydrofuran (100 mL) was treated with titanium (IV) chloride (10.43 g). During the dropwise addition of titanium (IV) chloride, the reaction mixture was cooled to maintain the temperature below 35°C. Upon complete addition, the resulting mixture was stirred at 30°C. After an additional 30 minutes, this mixture was treated with a solution of 2-methyl-2-propanethiol (6.76 mL) and triethylamine (16.70 mL) in tetrahydrofuran (15 mL). The resulting mixture was stirred at 50°C. After two hours, the mixture was added to ten percent sodium carbonate (500 mL). The resulting mixture was extracted with methylene chloride. The combined methylene chloride extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 17.2 g of an oil, which crystallized upon cooling to room temperature. This crystalline material was recrystallized from hot ethanol to give 12.3 g of the title compound. Melting point 71-73°C.

Analysis calculated for $C_{20}H_{24}O_2S$: C, 73.13; H, 7.36; S, 9.76. Found: C, 73.37; H, 7.51; S, 9.87.

B. Preparation of **E-*t*-Butyl 4,4'-Dimethoxystilbenyl Sulfoxide**

The crystalline compound prepared as described in Example 1A was dissolved in toluene (150 mL), and the resulting solution cooled to about -20°C. The cold solution was treated with peracetic acid (32% w/w in dilute acetic acid, 1.24 g) over ten minutes. The resulting mixture was

extracted with saturated sodium sulfite and brine. The organic phase was concentrated *in vacuo*. The residue was recrystallized from ethyl acetate/heptane to give 14.11 g of the title compound. Melting point 104°C (dec).

Analysis calculated for $C_{20}H_{24}O_3S$: C, 69.74; H, 7.02; S, 9.31. Found: C, 69.47; H, 7.04; S, 9.54.

Example 2

Z-*t*-Butyl 4,4'-Dimethoxystilbenyl Sulfoxide

A. Preparation of *t*-Butyl 4-Methoxybenzyl Sulfide

A mixture of 4-methoxybenzyl alcohol (10.13 g) and zinc iodide (11.7 g) in 1,2-dichloroethane (120 mL) was treated with 2-methyl-2-propanethiol (9.92 mL) in one portion. The resulting mixture was stirred at room temperature. After about 18 hours, the reaction was diluted with water (100 mL) and methylene chloride (100 mL). The organic phase was removed, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 14.4 g of an oil.

^{1}H NMR ($CDCl_3$): δ 7.28 (d, 2H), 6.85 (d, 2H), 3.77 (s, 3H), 3.73 (s, 2H), 1.36 (s, 9H).

^{13}C NMR ($CDCl_3$): δ 130, 114, 56, 35, 32.

Analysis calculated for $C_{12}H_{18}OS$: C, 68.52; H, 8.63. Found: C, 68.8; H, 8.67.

B. Preparation of **Z**-*t*-Butyl 4,4'Dimethoxystilbenyl Sulfide

A solution of the compound prepared as described in Example 2A (2.51 g) in tetrahydrofuran (50 mL) was cooled to about -20°C. This cold solution was treated with a solution of *n*-butyllithium in hexane (1.6 M, 7.47 mL) over ten minutes. The resulting solution was allowed to warm to about 0°C over 35 minutes. This cold solution was treated with *p*-anisaldehyde (1.46 mL). After an additional 15 minutes, the reaction solution was treated with methanesulfonyl chloride (0.95 mL). The resulting reaction was allowed to warm to room temperature. After an additional 45 minutes, the

reaction mixture was treated with a solution of potassium *t*-butoxide in tetrahydrofuran (1.0 M, 12.0 mL). After an additional 45 minutes, the reaction was quenched by the addition of 1N hydrochloric acid (12.0 mL). The organic phase was separated, dried over magnesium sulfate, filtered, and concentrated to an oil (4.4 g).

^{1}H NMR ($CDCl_3$): δ 7.95 (d, H), 7.05 (s, H), 6.9 (d, H), 6.8 (dd, 2H), 3.75 (s, 3H), 0.95 (s, 9H).

^{13}C NMR ($CDCl_3$): δ 153, 139, 137, 114, 56, 32.

C. Preparation of **Z**-*t*-Butyl 4,4'-Dimethoxystilbenyl Sulfoxide

The compound from Example 2B was converted to the title compound using the procedure substantially as described in Example 1B.

^{1}H NMR ($CDCl_3$): δ 7.61 (d, H), 7.56 (d, H), 7.1 (s, H), 6.9 (dd, 2H), 3.83 (s, 3H), 1.05 (s, 9H).

^{13}C NMR ($CDCl_3$): δ 142, 132.5, 131, 118, 117, 56, 24.

Analysis calculated for $C_{20}H_{24}O_3S$: C, 69.74; H, 7.02. Found: C, 69.98; H, 6.94.

Example 3

E and **Z**-*t*-Butyl 4,4'-Dimethoxystilbenyl Sulfoxide

A. Preparation of *t*-Butyl 4-Methoxybenzyl Sulfide

A mixture of 4-methoxybenzyl alcohol (10.13 g) and zinc iodide (11.7 g) in 1,2-dichloroethane (120 mL) was treated with 2-methyl-2-propanethiol (9.92 mL) in one portion. The resulting mixture was stirred at room temperature. After about 18 hours, the reaction was diluted with water (100 mL) and methylene chloride (100 mL). The organic phase was removed, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 14.4 g of an oil.

^{1}H NMR ($CDCl_3$): δ 7.28 (d, 2H), 6.85 (d, 2H), 3.77 (s, 3H), 3.73 (s, 2H), 1.36 (s, 9H).

^{13}C NMR ($CDCl_3$): δ 130, 114, 56, 35, 32.

Analysis calculated for $C_{12}H_{18}OS$: C, 68.52; H, 8.63. Found: C, 68.8; H, 8.67.

B. Preparation of *t*-Butyl 4-Methoxybenzyl Sulfoxide

A solution of the compound prepared as described in Example 3A (14.4 g) in 1,2-dichloroethane (50 mL) was cooled to about 5°C and the cold solution treated with peracetic acid (32% w/w in dilute acetic acid, 14.2 mL) over 30 minutes. Upon complete addition of the peracetic acid, the reaction was treated with brine and sodium bicarbonate. The organic phase was removed, dried over magnesium sulfate, filtered, and concentrated to a yellow precipitate. This residue was treated with hexane (100 mL) and the resulting mixture stirred at room temperature. After about 18 hours, the mixture was filtered and the solids washed with hexane (100 mL). The solid material was dried *in vacuo* to give 14.07 g of the title compound. Melting point 124-126°C.

^{1}H NMR ($CDCl_3$): δ 7.26 (d, 2H), 6.89 (d, 2H), 3.79 (d, H), 3.78 (s, 3H), 3.58 (d, H), 1.3 (s, 9H).

^{13}C NMR ($CDCl_3$): δ 132, 114, 56, 53, 23.

Analysis calculated for $C_{12}H_{18}O_2S$: C, 63.68; H, 8.02. Found: C, 63.72; H, 7.93.

C. Preparation of **E** and **Z**-*t*-Butyl 4,4'-Dimethoxystilbenyl Sulfoxide

A solution of the compound prepared as described in Example 3B (10.0 g) in tetrahydrofuran (140 mL) was cooled to about -30° to -25°C (dry ice/acetone bath). This cold solution was treated with *n*-butyllithium in cyclohexane (1.6 M, 27.65 mL) over 25 minutes. After stirring for 35 minutes, the reaction mixture was treated with *p*-anisaldehyde (5.4 mL). The dry ice/acetone bath was removed and the reaction allowed to warm to about 20°C. This mixture was treated with methanesulfonyl chloride (3.5 mL). The temperature of the reaction rose from about 20° to about 35°C

upon addition of the methanesulfonyl chloride. The mixture was cooled to about 25°C, then treated with potassium *t*-butoxide in tetrahydrofuran (1 M, 50.9 mL). After stirring for an additional 35 minutes, the reaction was treated with 1N hydrochloric acid (51.0 mL). The phases were separated, and the organic layer dried over magnesium sulfate, filtered, and concentrated to an oil (16.67 g). This material was used in the next step without further purification. The carbon and proton NMR spectra were similar to that obtained for the compound prepared as described in Examples 1 and 2.

Example 4

Z-*t*-Butyl 4,4'-Dimethoxystilbenyl Sulfoxide

A solution of the compound prepared as described in Example 3B (3.0 g) in tetrahydrofuran (40 mL) was cooled to about -15°C. This cold solution was treated with *n*-butyllithium in cyclohexane (1.6 M, 8.3 mL) over 15 minutes. After stirring for ten minutes, the reaction mixture was warmed to 0°C, and treated with *p*-anisaldehyde (1.61 mL). The ice bath was removed and the reaction allowed to warm to about room temperature. This mixture was treated with acetyl chloride (0.95 mL). After about one hour, the reaction mixture was treated with potassium *t*-butoxide in tetrahydrofuran (1 M, 16.0 mL). After stirring for an additional 1.5 hours, the reaction was treated with 1N hydrochloric acid (17.0 mL). The phases were separated, and the organic layer dried over magnesium sulfate, filtered, and concentrated to an oil (5.26 g). This material was used without further purification. The carbon and proton NMR spectra were similar to that obtained for the compound prepared as described in Example 2.

Example 5

6-Methoxy-2-(4-methoxyphenyl)benzo[b]thiophene

A solution of *p*-toluenesulfonic acid monohydrate

(2.25 g) in toluene (60 mL) was heated to reflux, and water was removed by allowing it to collect in a Dean-Stark trap. Using a nitrogen gas purge vented through the top of the condenser, a solution of the compound prepared as described in Example 1 (2.04 g) in toluene (33 mL) was added to the refluxing acid solution over 1.5 hours. The resulting mixture was cooled to about 5°C under the nitrogen purge, then treated with water (8 mL). The resulting slurry was stirred for three hours. The slurry was filtered, and the crystalline product washed with water (8 mL) and acetone (8 mL). The crystalline product was dried *in vacuo* at 40°C for about 18 hours to give 1.30 g of the title compound as a light tan solid. This compound was identical to the compound prepared by a published route. Melting Point 196-199°C.

Example 6

6-Methoxy-2-(4-methoxyphenyl)benzo[b]thiophene

A solution of *p*-toluenesulfonic acid monohydrate (2.49 g) in toluene (108 mL) was heated to reflux, and water was removed by allowing it to collect in a Dean-Stark trap. A solution of the compound prepared as described in Example 1 (9.00 g) in toluene (32 mL) was added to the refluxing acid solution over six hours. Upon complete addition, absolute ethanol (35 mL) was added to the reaction solution, and the resulting mixture was allowed to cool to room temperature. After about 18 hours, a precipitate was isolated by filtration. This precipitate was washed with toluene/ absolute ethanol (4:1, 29 mL), and dried *in vacuo* at 40°C for about 18 hours to give 4.86 g of a solid. This compound was identical to the compound prepared by a published route. Melting point 199-200°C.

Example 7

6-Hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)-benzoyl]benzo[b]thiophene Hydrochloride 1,2-Dichloroethane Solvate

A. Preparation of Ethyl 4-(2-Piperidinoethoxy)benzoate

A mixture of ethyl 4-hydroxybenzoate (8.31 g), 1-(2-chloroethyl)piperidine monohydrochloride (10.13 g), potassium carbonate (16.59 g), and methyl ethyl ketone (60 mL) was heated to 80°C. After one hour, the mixture was cooled to about 55°C and treated with additional 1-(2-chloroethyl)-piperidine monohydrochloride (0.92 g). The resulting mixture was heated to 80°C. The reaction was monitored by thin layer chromatography (TLC), using silica-gel plates and ethyl acetate/acetonitrile/triethylamine (10:6:1, v/v). Additional portions of 1-(2-chloroethyl)piperidine hydrochloride are added until the starting 4-hydroxybenzoate ester is consumed. Upon complete reaction, the reaction mixture was treated with water (60 mL) and allowed to cool to room temperature. The aqueous layer was discarded and the organic layer concentrated *in vacuo* at 40°C and 40 mm Hg. The resulting oil was used in the next step without further purification.

B. Preparation of 4-(2-Piperidinoethoxy)benzoic Acid Hydrochloride

A solution of the compound prepared as described in Example 7A (about 13.87 g) in methanol (30 mL) was treated with 5 N sodium hydroxide (15 mL), and heated to 40°C. After 4 1/2 hours, water (40 mL) was added. The resulting mixture was cooled to 5-10°C, and concentrated hydrochloric acid (18 mL) was added slowly. The title compound crystallized during acidification. This crystalline product was collected by filtration, and dried *in vacuo* at 40-50°C to give 83% yield of the title compound. Melting point 270-271°C.

C. Preparation of 4-(2-Piperidinoethoxy)benzoyl Chloride Hydrochloride

A solution of the compound prepared as described in Example 7B (30.01 g) and dimethylformamide (2 mL) in methylene chloride (500 mL) was treated with oxalyl chloride (10.5 mL) over a 30-35 minute period. After stirring for about 18 hours, the reaction was assayed for completion by HPLC analysis. Additional oxalyl chloride may be added to the reaction if the starting carboxylic acid is present. Upon completion, the reaction solution was evaporated to dryness *in vacuo*. The residue was dissolved in methylene chloride (200 mL), and the resulting solution evaporated to dryness. This dissolution/evaporation procedure was repeated to give the title compound as a solid. The title compound may be stored as a solid or as a 0.2 M solution in methylene chloride (500 mL).

D. Preparation of 6-Hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene Hydrochloride 1,2-Dichloroethane Solvate

A mixture of the compound prepared as described in Example 5 or 6 (2.92 g), the compound prepared as described in Example 7C (3.45 g), and 1,2-dichloroethane (52 mL) was cooled to about 0°C. Boron trichloride gas was condensed into a cold graduated cylinder (2.8 mL), and added to the cold mixture described above. After eight hours at 0°C, the reaction mixture was treated with additional boron trichloride (2.8 mL). The resulting solution was heated to 35°C. After 16 hours, the reaction was complete.

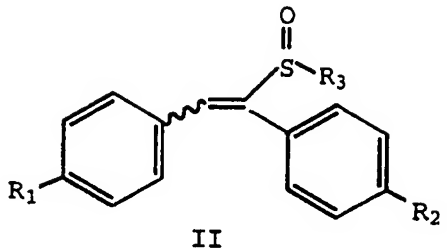
Methanol (30 mL) was treated with the reaction mixture from above over a 20-minute period, causing the methanol to reflux. The resulting slurry was stirred at 25°C. After one hour, the crystalline product was filtered, washed with cold methanol (8 mL), and dried at 40°C *in vacuo* to give 5.14 g of the title compound. Melting point 225°C.

Potency: 86.8%

1,2-Dichloroethane: 6.5% (gas chromatography)

We claim:

1. A compound of the formula



II

wherein:

R_1 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino;

R_2 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino; and

R_3 is a thermally-labile or acid-labile C_2-C_{10} alkyl, C_4-C_{10} alkenyl, or aryl(C_1-C_{10} alkyl) group.

2. A compound as claimed in Claim 1 wherein:

R_1 is hydrogen, C_1-C_4 alkoxy, or arylalkoxy; and

R_2 is hydrogen, C_1-C_4 alkoxy, or arylalkoxy.

3. A compound as claimed in Claim 2 wherein R_3 is a thermally-labile or acid-labile C_2-C_{10} alkyl or aryl(C_1-C_{10} alkyl) group.

4. A compound as claimed in Claim 3 wherein R_3 is a thermally-labile or acid-labile C_2-C_{10} alkyl group.

5. A compound as claimed in Claim 4 wherein:

R_1 is hydrogen or C_1-C_4 alkoxy; and

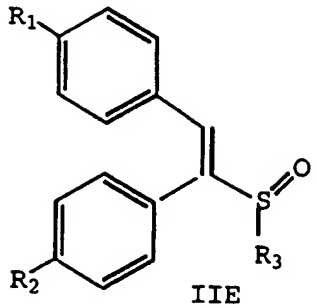
R_2 is hydrogen or C_1-C_4 alkoxy.

6. A compound as claimed in Claim 5 wherein R_1 and R_2 are C_1-C_4 alkoxy.

7. A compound as claimed in Claim 6 wherein R_3 is *t*-butyl.

8. A compound as claimed in Claim 5 wherein R_1 and R_2 are methoxy.

9. A compound as claimed in Claim 1 of the formula



IIE

wherein:

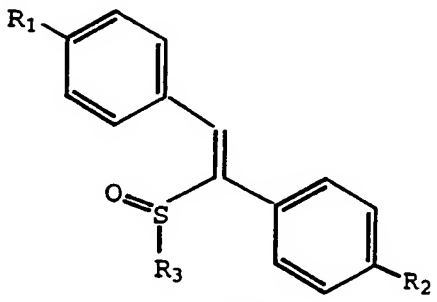
R_1 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino;

R_2 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino; and

R_3 is a thermally-labile or acid-labile C_2-C_{10} alkyl, C_4-C_{10} alkenyl, or aryl(C_1-C_{10} alkyl) group.

10. A compound as claimed in Claim 10 wherein R_1 and R_2 are methoxy, and R_3 is *t*-butyl.

11. A compound as claimed in Claim 1 of the formula



IIZ

wherein:

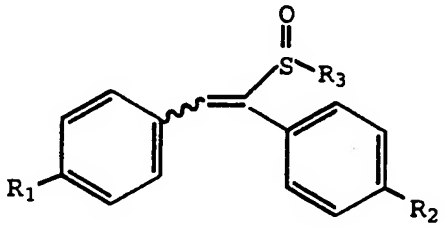
R_1 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino;

R_2 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino; and

R_3 is a thermally-labile or acid-labile C_2-C_{10} alkyl, C_4-C_{10} alkenyl, or aryl(C_1-C_{10} alkyl) group.

12. A compound as claimed in Claim 11 wherein R_1 and R_2 are methoxy, and R_3 is *t*-butyl.

13. A process for preparing a compound of the formula



II

wherein:

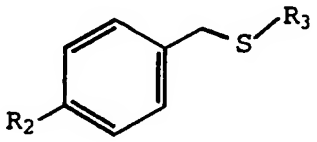
R_1 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino;

R_2 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino; and

R_3 is a thermally-labile or acid-labile C_2-C_{10} alkyl, C_4-C_{10} alkenyl, or aryl(C_1-C_{10} alkyl) group having a tertiary carbon atom adjacent to the sulfur atom;

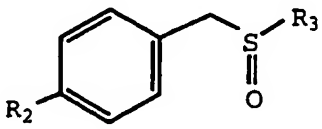
comprising the steps of:

(1) oxidizing a benzyl sulfide of the formula:



wherein R_2 and R_3 are as defined above;

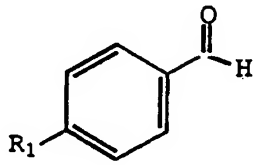
with an oxidizing agent to produce a benzyl sulfoxide of the formula:



wherein R_2 and R_3 are as defined above;

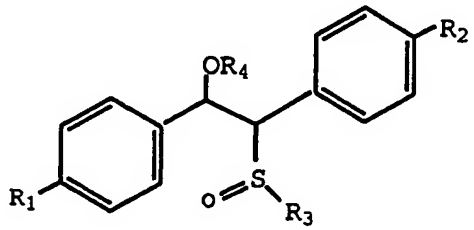
(2) reacting said benzyl sulfoxide with a first strong base to form a benzylic anion;

(3) condensing said benzylic anion with a benzaldehyde of the formula



wherein R_1 is as defined above;

(4) reacting the condensation product from step 3 with an acid chloride to produce an ester of the formula



wherein:

R_1, R_2, and R_3 are as defined above; and

R_4 is $CO(C_1\text{-}C_6$ alkyl), CO(aryl), CO(arylalkyl), $SO_2(C_1\text{-}C_6$ alkyl), SO_2(aryl), SO_2(arylalkyl), $CO_2(C_1\text{-}C_6$ alkyl), CO_2(aryl), CO_2(arylalkyl), or $CON(C_1\text{-}C_6$ alkyl$)_2$; and

(5) treating said ester with a second strong base.

14. The process of Claim 13 wherein:

R_1 is hydrogen, $C_1\text{-}C_4$ alkoxy, or arylalkoxy; and

R_2 is hydrogen, $C_1\text{-}C_4$ alkoxy, or arylalkoxy.

15. The process of Claim 14 wherein R_3 is a thermally-labile or acid-labile $C_2\text{-}C_{10}$ alkyl or aryl($C_1\text{-}C_{10}$ alkyl) group, having a tertiary carbon atom adjacent to the sulfur atom.

16. The process of Claim 15 wherein the oxidizing agent is peracetic acid.

17. The process of Claim 16 wherein the first stong base is an alkyllithium.

18. The process of Claim 17 wherein the first strong base is *n*-butyllithium.

19. The process of Claim 17 wherein the acid chloride is a sulfonyl chloride, and R_4 is $SO_2(C_1\text{-}C_6$ alkyl), SO_2(aryl), or SO_2(arylalkyl)..

20. The process of Claim 19 wherein the sulfonyl chloride is methanesulfonyl chloride.

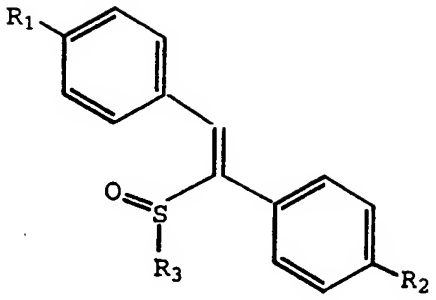
21. The process of Claim 17 wherein the second strong base is a metal alkoxide.

22. The process of Claim 19 wherein the metal alkoxide is potassium *t*-butoxide..

23. The process of Claim 22 wherein R_3 is a thermally-labile or acid-labile $C_2\text{-}C_{10}$ alkyl group, having a tertiary carbon atom adjacent to the sulfur atom.

24. The process of Claim 17 wherein R_1 and R_2 are methoxy, and R_3 is *t*-butyl.

25. A process for preparing a compound of the formula



IIZ

wherein:

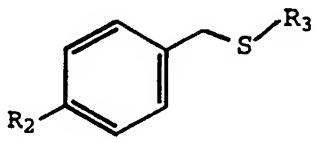
R_1 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino;

R_2 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino; and

R_3 is a thermally-labile or acid-labile C_2-C_{10} alkyl, C_4-C_{10} alkenyl, or aryl(C_1-C_{10} alkyl) group having a tertiary carbon atom adjacent to the sulfur atom;

comprising the steps of:

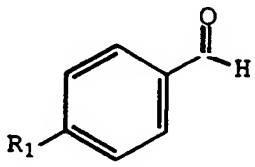
(1) reacting a benzyl sulfide of the formula:



wherein R_2 and R_3 are as defined above;

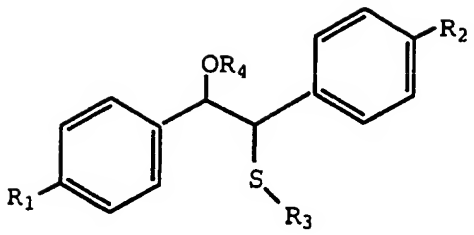
with a first strong base to form a benzylic anion;

(2) condensing said benzylic anion with a benzaldehyde of the formula



wherein R_1 is as defined above;

(3) reacting the condensation product from step 2 with an acid chloride to produce an ester of the formula

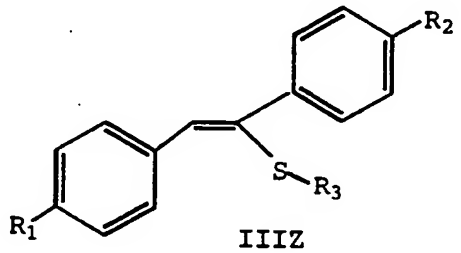


wherein:

R_1, R_2, and R_3 are as defined above; and

R_4 is $CO(C_1-C_6$ alkyl), CO(aryl), CO(arylalkyl), $SO_2(C_1-C_6$ alkyl), SO_2(aryl), SO_2(arylalkyl), $CO_2(C_1-C_6$ alkyl), CO_2(aryl), CO_2(arylalkyl), or $CON(C_1-C_6$ alkyl$)_2$;

(4) treating said ester with a second strong base to produce a styryl sulfide of the formula;



IIIZ

wherein R_1, R_2, and R_3 are as defined above; and

(5) oxidizing said styryl sulfide with an oxidizing agent.

26. The process of Claim 25 wherein:

R_1 is hydrogen, C_1-C_4 alkoxy, or arylalkoxy; and

R_2 is hydrogen, C_1-C_4 alkoxy, or arylalkoxy.

27. The process of Claim 26 wherein R_3 is a thermally-labile or acid-labile C_2-C_{10} alkyl or aryl(C_1-C_{10} alkyl) group, having a tertiary carbon atom adjacent to the sulfur atom.

28. The process of Claim 26 wherein the oxidizing agent is peracetic acid.

29. The process of Claim 28 wherein the first stong base is an alkyllithium.

30. The process of Claim 29 wherein the first strong base is *n*-butyllithium.

31. The process of Claim 29 wherein the acid chloride is a sulfonyl chloride, and R_4 is $SO_2(C_1\text{-}C_6$ alkyl), SO_2(aryl), or SO_2(arylalkyl).

32. The process of Claim 31 wherein the sulfonyl chloride is methanesulfonyl chloride.

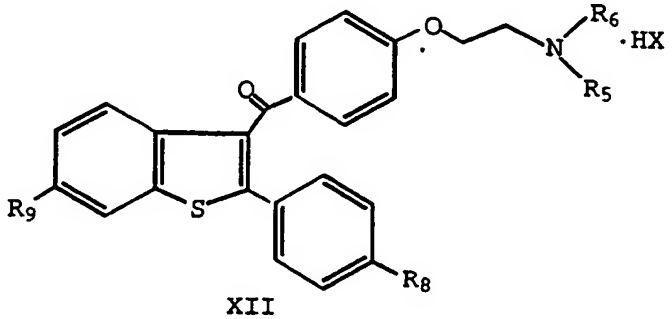
33. The process of Claim 29 wherein the second strong base is a metal alkoxide.

34. The process of Claim 33 wherein the metal alkoxide is potassium *t*-butoxide.

35. The process of Claim 34 wherein R_3 is a thermally-labile or acid-labile $C_2\text{-}C_{10}$ alkyl group, having a tertiary carbon atom adjacent to the sulfur atom.

36. The process of Claim 29 wherein R_1 and R_2 are methoxy, and R_3 is *t*-butyl.

37. A process for preparing a compound of the formula



XII

wherein:

R_8 is hydrogen, halo, amino, or hydroxyl;

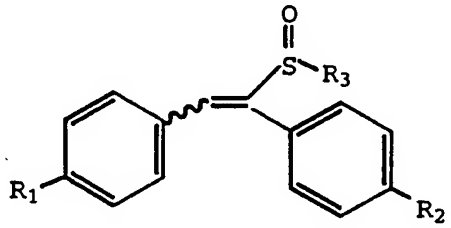
R_9 is hydrogen, halo, amino, or hydroxyl;

R_5 and R_6 are independently C_1-C_4 alkyl, or R_5 and R_6 together with the adjacent nitrogen atom form a heterocyclic ring selected from the group consisting of pyrrolidino, piperidino, hexamethyleneimino, and morpholino; and

HX is HCl or HBr;

comprising the steps of:

(a) cyclizing in the presence of an acid catalyst a compound of the formula



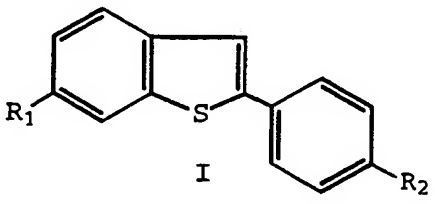
II

wherein:

R_1 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino;

R_2 is hydrogen, C_1-C_4 alkoxy, arylalkoxy, halo, or amino; and

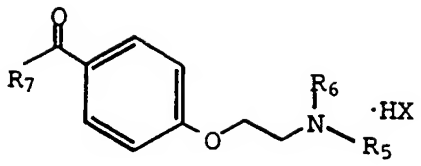
R_3 is a thermally-labile or acid-labile C_2-C_{10} alkyl, C_4-C_{10} alkenyl, or aryl(C_1-C_{10} alkyl) group to prepare a benzothiophene compound of the formula



I

wherein R_1 and R_2 are as defined above;

(b) acylating said benzothiophene compound with an acylating agent of the formula



wherein:

R_5, R_6, and HX are as defined previously; and

R_7 is chloro, bromo, or hydroxyl; in the presence of BX'_3, wherein X' is chloro or bromo;

(c) when R_1 and/or R_2 is C_1-C_4 alkoxy or arylalkoxy, dealkylating one or more phenolic groups of the acylation product of step (b) by reacting with additional BX'_3, wherein X' is as defined above; and

(d) optionally isolating the formula XII compound.

INTERNATIONAL SEARCH - REPORT

International application No.
PCT/US96/09163

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07F 7/08, 7/18
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 556/428; 558/62; 564/102; 568/23, 25; 540/604; 544/158; 546/192, 236; 548/542

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 5,514,826 A (HOARD ET AL) 07 May 1996, see the entire document.	1-37

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 JULY 1996	04 SEP 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer FREDERICK KRASS Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH - REPORT

International application No.
PCT/US96/09163

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.